REMARKS

Claims 13 to 41 are pending with claims 13, 21 to 23 and 25 to 27 withdrawn from consideration as drawn to a non-elected invention. Therefore, claims 14 to 20, 24 and 28 to 41 are presently under examination.

Regarding the Amendments

Claims 14, 15, 17, 19, 24, 28, 30, 32, 34, 36, 38, and 40 have been amended to indicate that the claimed peptides are in isolated form. The amendment is supported in the specification, for example, at page 39, lines 4-6 (Example II C), which indicates that the brain homing peptide, CLSSRLDAC (SEQ ID NO: 3) was synthesized and purified by HPLC (see, also, page 40 lines 4-12).

Claims 15, 17, 19, 28, 30, 32, 34, 36, 38, and 40 have been amended to delete the phrase "that selectively homes to brain" from the preamble. This amendment to the preamble does not add new matter and does not narrow the scope of the claims.

As set forth above, the amendments are supported by the specification and do not add new matter. Accordingly, Applicants respectfully request that the Examiner enter the amendments.

Regarding the Election/Restriction

Claims 13, 21 to 23 and 25 to 27 are withdrawn from consideration as being drawn to a nonelected invention. Applicants respectfully request that these claims be held in abeyance until allowable subject matter is determined.

Regarding the Rejection under 35 U.S.C. § 101

The rejection of claims 14 to 20, 24 and 28 to 41 under 35 U.S.C. § 101 respectfully is traversed. The Office Action indicates that the claims encompass naturally-occurring entities and, therefore, are directed to non-statutory subject matter.

Applicants note that the claims as amended are directed to "isolated" peptides, which can be, for example, produced recombinantly or synthetically, or can be naturally occurring molecules purified, for example, from a cell using biochemical methods. Thus, as amended, the claims are directed to statutory subject matter. In view of the above amendments and remarks, Applicants respectfully request that the Examiner remove the rejection of claims 14 to 20, 24 and 28 to 41 under 35 U.S.C. § 101.

Regarding the Rejection under 35 U.S.C. § 112, first paragraph

The rejection of claims 14 to 20, 24 and 28 to 41 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement respectfully is traversed. The Office Action indicates that the

specification only enables small peptides that selectively home, for example, SEQ ID NOS:1 to 3 and 16 and alleges that no peptides other than the specific, disclosed SRL or VLR peptides, no large peptides and no peptides containing a certain motif have been enabled. Applicants respectfully disagree for the reasons which follow.

Applicants submit that, in view of the guidance provided by the specification, undue experimentation would not have been required to practice the full scope of the invention. Guidance is provided in the specification, which discloses *in vivo* panning experiments directed to selective homing in the brain. Of 73 cloned phage recovered from brain, peptides containing an SRL motif predominated (36% of the clones sequenced) followed by peptides containing the VLR motif (20.5%; see page 34, lines 13-16). Additional guidance to the skilled person is provided by Table 1, which discloses the SRL-containing peptides CNSRLHLRC (SEQ ID NO: 1), CLSSRLDAC (SEQ ID NO: 3) and CNSRLQLRC (SEQ ID NO: 5), and the VLR-containing peptides CVLRGGRC (SEQ ID NO: 4) and WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16; see page 36). When assayed for accumulation in brain and kidney, SEQ ID NO: 1 and 3 were about 8-fold enriched in brain as compared to kidney, and SEQ ID NO: 16 was about 9-fold more enriched in brain than in kidney (page 35, line 3, to page 37, line 9). Thus, the specification provides guidance regarding a variety of X_1SRLX_2 or X_3VLRX_4 peptides that exhibit at least two-fold greater specific binding to brain than to kidney as recited in claims 14 and 24.

Furthermore, the disparate amino acid residues flanking the recited SRL or VLR motif corroborate to one skilled in the art that the claimed X_1SRLX_2 or X_3VLRX_4 peptides have selective homing activity when a variety of different X_1, X_2, X_3 and X_4 flanking sequences are present. As shown in Table 1 (page 36), the VLR-containing peptides CVLRGGRC (SEQ ID NO: 4) and WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16) were recovered from brain. As can be seen by comparing the residues immediately adjacent to the VLR motif in the X_4 portion of X_3VLRX_4, the peptide CVLRGGRC (SEQ ID NO: 4) contains the small, non-charged amino acid residue glycine (G), while, in contrast, the same position in SEQ ID NO: 16 is occupied by the negatively charged amino acid residue glutamate (E). Moreover, the X_4 portion of SEQ ID NO: 4 contains only 4 amino acid residues, while the X_4 portion of SEQ ID NO: 16 is longer, containing 15 residues. Furthermore, as can be seen by comparing the residues in the X_3 portion of SEQ ID NOS; 16 and 4, peptide SEQ ID NO: 16 contains the positively charged amino acid residue arginine (R), while SEQ ID NO: 4 contains no such charged residue in the X_3 portion. These results corroborate that a variety of X_3 and X_4 sequences can be present in a X_3VLRX_4 peptide of the invention that selectively homes to brain.

A similar comparison can be made of the amino acid residues flanking the SRL motif in the X_1SRLX_2 (SEQ ID NO: 45) peptides of the invention. The SRL-containing peptides CNSRLHLRC (SEQ ID NO:1), CLSSRLDAC (SEQ ID NO:3), and CNSRLQLRC (SEQ ID NO:5) were recovered by *in vivo* panning on brain (page 36, Table 1), with a brain to kidney homing ratio of about 8 for SEQ ID

NOS: 1 and 3. Comparison of the residues immediately adjacent to the SRL motif in the X_2 portion of X_1SRLX_2 (SEQ ID NO: 45) reveals that SEQ ID NO: 1 contains the moderately positively charged amino acid residue histidine (H), while, in contrast, the same position in SEQ ID NO: 3 is occupied by the negatively charged amino acid residue aspartic acid (D), and the equivalent position in SEQ ID NO: 5 is occupied by the uncharged amino acid residue glutamine (Q). Furthermore, as can be seen by comparing the residues in the X_1 portion, SEQ ID NO: 3 contains the large, hydrophobic amino acid residue leucine (L), while the X_1 portion of SEQ ID NOS: 1 and 5 contains no such hydrophobic residue. These results confirm that a variety of different X_1 and X_2 sequences can be present in a X_1SRLX_2 peptide of the invention that selectively homes to brain. In view of the diverse amino acid sequences X_1, X_2, X_3 and X_4 that flank the recited SRL and VLR motifs in peptides disclosed in the specification, one skilled in the art understands that selective homing activity is at least largely independent of the flanking sequence.

Applicants further submit that, in view of the guidance in the specification, only routine experimentation would have been required for the skilled person to make a X_1SRLX_2 (SEQ ID NO: 45) or X_3VLRX_4 (SEQ ID NO: 46) peptide and to confirm that it exhibits at least two-fold greater specific binding to brain than to kidney. The skilled artisan would have been able to make a X_1SRLX_2 (SEQ ID NO: 45) or X_3VLRX_4 (SEQ ID NO: 46) peptide by routine chemical synthesis or standard recombinant methods well known in the art at the time the invention was made, or have such a peptide prepared and purified commercially (see page 7,

lines 17-19; and page 39, lines 4-7). The skilled artisan also would have been able to prepare a "focused" phage library that displays an X_1SRLX_2 or X_3VLRX_4 peptide with a variety of flanking sequences. Methods of preparing a phage display library including a focused library containing a fixed "SRL" or "VLR" motif were routine and well known in the art at the time the invention was made (see, for example, specification at page 31, lines 1-32). Thus, undue experimentation would not have been required to prepare a variety of X_1SRLX_2 or X_3VLRX_4 peptides.

Neither would undue experimentation have been required for the skilled person to corroborate that a particular X_1SRLX_2 or X_3VLRX_4 peptide exhibited at least two-fold greater specific binding to brain than to kidney as recited in claims 14 and 24. For example, to corroborate specific binding, a X_1SRLX_2 or X_3VLRX_4 peptide can be labeled with ^{125}I as set forth in the specification, injected into the tail vein of a mouse, and the amount of radioactivity determined in brain and kidney after these organs are harvested. Such work requires only routine techniques, as set forth in the specification at page 40, lines 4-22. Additional routine techniques for confirming at least two-fold greater specific binding also are taught in the subject application. The specification teaches, for example, that phage displaying a X_1SRLX_2 or X_3VLRX_4 peptide of interest can be prepared, and then amplified and administered to mice, following which brain and kidney can be removed and the number of transforming units of phage determined in each organ (see page 31, lines 2-32, and page 35, lines 3-15). Again, the work required to corroborate that a phage-displayed X_1SRLX_2 or X_3VLRX_4

peptide exhibits at least two-fold greater specific binding to brain than to kidney would have been performed with well known standard phage methods using the guidance provided in the specification.

In sum, in view of the guidance provided by the specification, only routine techniques and not undue experimentation would have been required to enable the full scope of the X_1SRLX_2 and X_3VLRX_4 peptides of the invention. Applicants therefore respectfully request that the Examiner remove the enablement rejection of claims 15 to 20, 24 and 28 to 41.

Regarding enablement of large peptides

The Office Action indicates that no large peptides have been demonstrated to selectively home, and, therefore, that large peptides are not enabled.

Applicants submit that the specification supports the selective brain homing activity of the recited SRL and VLR motifs in the context of a larger molecule. Firstly, Applicants note that phage displayed peptides were expressed on the surface of a phage particle as a fusion protein with the gene III protein as disclosed in Example I, thus placing the homing peptides in the context of a significantly larger molecule (see page 31, lines 22-25). These peptides had selective brain homing activity as indicated by a brain:kidney homing ratio of greater than two; see, for example, page 37, lines 1-9, which indicates that the ratio of selective brain:kidney homing was about 8 for the

SRL-containing peptides SEQ ID NOS: 1 and 3, and about 9 for the VLR-containing peptide SEQ ID NO: 16. Thus, phage-displayed peptides fused to the larger gene III protein resulted in selective brain homing of phage expressing the homing peptide/gene III fusion protein. Secondly, Applicants direct the Examiner's attention to conjugation of the brain homing peptide CLSSRLDAC (SEQ ID NO: 3) to red blood cells as further corroboration that the claimed X_1SRLX_2 (SEQ ID NO: 45) or X_3VLRX_4 (SEQ ID NO: 46) peptides have selective brain homing activity in the context of a larger molecule. After ^{125}I-labeled peptide/red blood cell conjugate was administered via the tail vein, approximately twice as much of CLSSRLDAC (SEQ ID NO: 3)/RBC complex was present in harvested brain as in kidney (page 34, lines 33-22). Co-administration of unlabeled synthetic peptide CLSSRLDAC (SEQ ID NO: 3) with the peptide-RBC complex inhibited homing of the complex to the brain but had no effect on homing to kidney (page 34, lines 22-27). These results demonstrate that an X_1SRLX_2 (SEQ ID NO: 45) or X_3VLRX_4 (SEQ ID NO: 46) peptide of the invention can maintain selective brain homing activity in a larger peptide or other molecule, for example, on the surface of a cell.

Also in regard to enablement of large peptides, the Office Action alleges that the size of the homing peptide impacts its ability to cross the blood-brain barrier and that only small peptide molecules are capable of mobilizing to the brain. The Office Action cites Kandel et al., Ed., Principles of Neural Science, Elsevier, 1991, page 1056, column 1, lines 28-46, to support this position. Applicants assert that the results

described above, namely the selective brain homing activity of peptides fused to the larger gene III protein and selective brain homing activity of a peptide/red blood cell conjugate demonstrate that the claimed X_1SRLX_2 (SEQ ID NO: 45) or X_3VLRX_4 (SEQ ID NO: 46) peptides can have selective brain homing activity even when X1, X2, X3 and X4 are of the maximal length. Again, because peptides or peptide/red blood cell conjugates were administered via the tail vein and recovered from the brain, these results demonstrate that the peptides and peptide-conjugates can cross the blood-brain barrier.

In view of the above, Applicants submit that the specification enables the full scope of the invention and, accordingly, respectfully request that the Examiner remove this ground for rejection.

Regarding selective homing

As a further ground for rejecting the claims as allegedly lacking enablement, the Office Action alleges that the examples only disclose localization in brain versus kidney and that, therefore, "selective homing" has not been demonstrated. The Office Action further indicates that "selective homing" indicates that the peptide is more abundant in brain than in any other control organ.

Applicants respectfully disagree with the Examiner's statement. As set forth in the specification, a molecule that selectively homes binds relatively specifically to a target

molecule present in one or a few selected organs following administration to a subject; such selective homing generally is characterized, in part, by at least a 2-fold (2x) greater specific binding of the molecule to the selected organ as compared to a control organ (page 15, lines 5-12). In view of the above, a peptide that selectively homes to brain can bind to one or a few other organs in addition to brain; absolute specificity of homing to brain is not required. Thus, it is not necessary that Applicants demonstrate that absence of homing to each and every organ other than brain.

Applicants further draw the Examiner's attention to the amendment to claims 15, 17, 19, 28, 30, 32,34, 36, 38 and 40, deleting the phrase "that selectively homes to brain" from the preamble. In view of the amendment, this ground for rejecting the claims does not apply to claims 15, 17, 19, 28, 30, 32,34, 36, 38 and 40.

Furthermore, claims 14 and 24, which recite the phrase "that selectively home to brain," previously have been amended to indicate that the claimed peptide "exhibits at least two-fold greater specific binding to brain than to kidney." Thus, as amended, the claims indicate that the selective homing has been measured using kidney as the control organ. Applicants note that, in contrast to the assertion in the Office Action, the language "exhibits at least two-fold greater specific binding to brain than to kidney" is recited in rejected independent claims 14 and 24. In view of the above remarks and amendments,

Applicants respectfully request that this ground for rejecting claims 14 and 24 be removed.

Having addressed each of the grounds for rejecting the claims as allegedly lacking enablement, Applicants submit that the full scope of the claims is enabled. Accordingly, Applicants respectfully request that the Examiner remove the enablement rejection of claims 14 to 20, 24 and 28 to 41 under 35 U.S.C. § 112, first paragraph.

Regarding the Rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 15 to 20 and 28 to 41 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to the phrase "selectively homes to the brain" respectfully is traversed. The Office Action alleges that the metes and bounds of the term "selectively homes to the brain" are indistinct.

Applicants submit that, in view of the specification, the term "selectively homes" is clear and definite to the skilled person. As defined in the specification, a molecule that "selectively homes" to an organ binds relatively specifically to a target molecule present in one or a few selected organs (page 15, 5-9). Furthermore, a molecule that "selectively homes" generally is characterized by at least a two-fold greater specific binding of the molecule to the selected organ as compared to a control organ (page 15, lines 9-12). In this regard, several X_1SRLX_2 (SEQ ID NO: 45) and X_3VLRX_4 (SEQ ID NO: 46) peptides that "selectively home to brain" were demonstrated

to be enriched in brain as compared to the control organ, kidney. The specification discloses that the enrichment ratio of several individual phage recovered from the selected organ, brain, was compared to kidney for SEQ ID NO: 1, 3 and 16; an 8-fold ratio of brain to kidney binding was seen for the SRL-containing peptides SEQ ID NOS: 1 and 3; and a 9-fold ratio of brain to kidney homing was seen for the VLR-containing peptide SEQ ID NO: 16 (page 37, lines 1-9). Thus, each of the brain homing peptides characterized exhibited at least two-fold greater specific binding to brain than to kidney, consistent with the definition of "selective homing" in the specification. In view of what is set forth in the specification, Applicants submit that the term "selectively homes" is clear and definite to the skilled person.

Although Applicants maintain that claims 14 and 24 are clear and definite as written, these claims previously have been amended to more clearly indicate that the claimed peptide "exhibits at least two-fold greater specific binding to brain than to kidney." This amendment, which was made to more clearly indicate that the language in the specification is a limitation of the claim, does not narrow the claim. In view of the amendment to claims 14 and 24 to more clearly indicate that the control organ is kidney and in view of the amendment to claims 15, 17, 19, 28, 30, 32, 34, 36, 38 and 40 to delete the phrase "that selectively homes to brain," Applicants submit that these claims are clear and definite and respectfully request that the Examiner remove the rejection of claims 15 to 20 and 28 to 41 under 35 U.S.C. § 112, second paragraph.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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